Clinical profile and outcome of children admitted with dengue fever in a tertiary care hospital in South India

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ABSTRACT

Objective: The objective is to study the clinical profile and outcome of patients admitted with dengue fever and to identify the risk factors for severe dengue (SD). **Materials and Methods:** This is a descriptive study of children admitted with a diagnosis of dengue fever from January 2013 to June 2014 in a tertiary care Medical College Hospital in South India. **Results:** A total of 306 children were admitted with dengue fever during the study period with a mean age of 7.8±3.2 years and male:female ratio of 1.06:1. The most common symptoms apart from fever were vomiting (54.9%) and abdominal pain (36.3%). Tender hepatomegaly and narrow pulse pressure were the most common signs. 131 (42.8%) were classified as dengue fever without warning signs, 119 (38.8%) as dengue fever with warning signs (DWS), and 56 (18.4%) as severe dengue (SD) according to the WHO guidelines 2012. A significant difference in aspartate aminotransferase' and alanine aminotransferase elevation was noted among dengue fever without warning signs, DWS, and SD. Hemoconcentration, thrombocytopenia, hypoproteinemia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hepatic derangement, elevated urea, and creatinine were significantly associated with SD. The mean values of prothrombin time, international normalized ratio, and activated partial thromboplastin time in SD were 19±3.7 s, 1.5±0.3 s, and 46±7 s, respectively. The finding of thalamic hypodensity in one patient with dengue encephalopathy was only rarely described in literature. **Conclusion:** Bleeding manifestations altered coagulation profile as well as deranged liver functions can be used as predictors of severe dengue fever.

Key words: *Dengue fever, Dengue with warning signs, Severe dengue*

In 2012, dengue ranks as the most important mosquito-borne disease in the world. Outbreaks exert a huge burden on populations, health systems, and economies [1]. In spite of the fact that in India, dengue was first reported in 1940s, the first case of confirmed dengue infection from Kerala was recorded in 1997 only [2]. However, Kerala has become hyperendemic for dengue fever in the past two decades [3]. Disease incidence and deaths are the highest in children aged ≤15 years [4]. Dengue fever is classified according to the revised WHO classification as dengue without warning signs (D), dengue with warning signs (DWS), and severe dengue (SD) [5]. The clinical presentation and severity change over the years. There are very few studies describing the clinical profile of children with dengue fever in Kerala, especially with regard to severity as per the WHO classification 2012. The present study was conducted in children admitted with dengue fever in a tertiary care government medical college in Kerala from January 2013 to June 2014 to look for the factors associated with SD.

MATERIALS AND METHODS

This was a descriptive study of children below 12 years of age admitted with the diagnosis of dengue fever in pediatric ward and intensive care unit. Children with pre-existing bleeding disorder, chronic liver disease, and proven viral hepatitis A or B were excluded from the study. All children satisfying the inclusion criteria were included in the study after getting prior written informed consent. They were thoroughly evaluated with detailed history and physical examination including nutritional status (assessed as per the Indian Academy of Pediatrics classification) such as complete blood count, packed cell volume, coagulation profile (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT]), and liver and renal function tests. The dengue non-structural protein 1 (NS1) antigen was done in children who presented in the 1st 5 days of illness. Dengue immunoglobulin (Ig) M and IgG were done after the 5th day of illness. Radiological evaluation such as X-ray chest, ultrasound abdomen, and computed tomography (CT) scan head was done wherever necessary.

Regular monitoring was done in all patients daily till discharge. The study population was classified as dengue fever without warning signs, dengue fever with warning signs (DWS), and SD according to the WHO guidelines 2012 (Fig. 1). They were also grouped into severe and non-SD to compare the baseline characteristics and coagulation abnormalities. In the

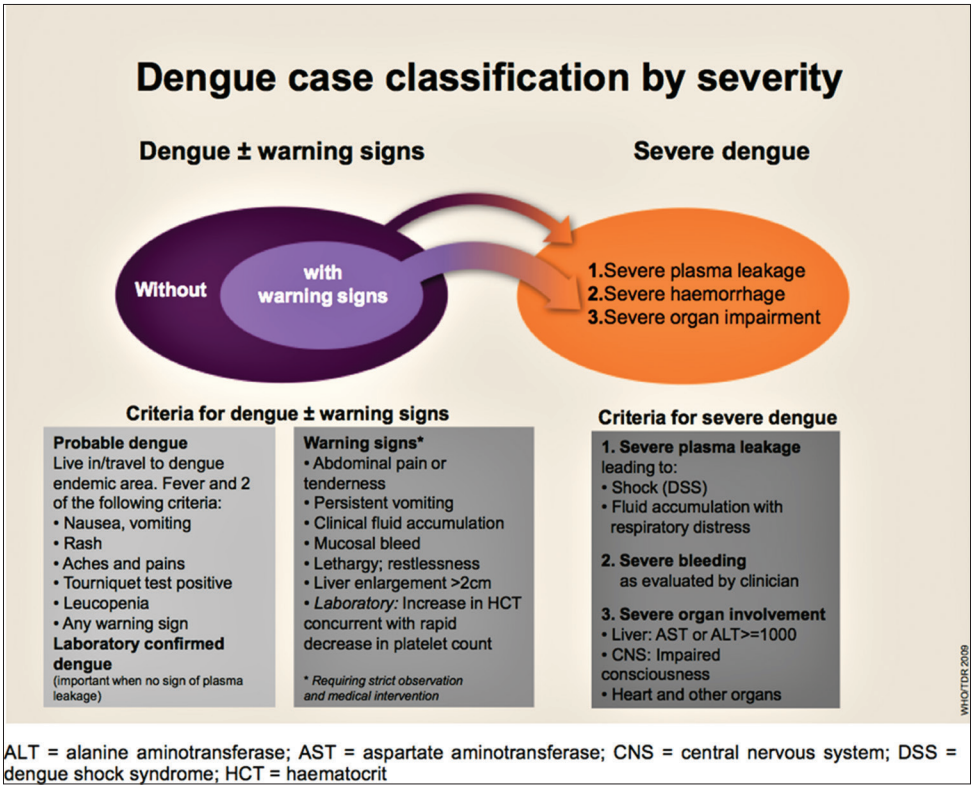

Figure 1: Dengue case classification by sererity WHO 2012 (Ref.5). AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CNS: Central nervous system, DSS: Dengue shock syndrome, HCT: Hematocrit

subset of cases where IgG was done, cases were classified as primary and secondary dengue based on IgG/Ig M ratio>1.1 [6]. The sample size was calculated as 300 based on a previous study using the formula $4pq/l^2$=284 (prevalence p=26%, q=100 –p=74, l=20% of p) [7].

Results for continuous variables were expressed as means and standard deviation. Categorical variables were expressed as percentages. Student's t-test for continuous variables and Chi-square test for discrete variables were used to test significance. The $p<0.05$ was considered statistically significant. The SPSS 22 software was used for statistical analysis.

RESULTS

A total of 306 children admitted with a diagnosis of dengue fever during the study period. Of 306 cases, majority 175 (57%) were in the age group of 6–12 years, 84 (27%) in the age group of 1–5 years, and 47 (16%) were infants. The mean age of the study population was estimated to be 7.8±3.2 years. Males were more in number (158) than females (148) with a male:female ratio of 1.06:1. A total of 216 (70.6%) children had normal nutritional status, 77 (25%) had Grade 1 malnutrition, and 13 (4.2%) had Grade 2 malnutrition.

Fever was present in all patients, with the duration of hospital stay <5 days in 205 (72%) and 5–10 days in 75 patients (25%). The most common symptoms were vomiting in 168 (54.90%), abdominal pain in 111 (36.3%), bleeding manifestation in 43(14.05%), headache in 41(13.40%), myalgia in 32 (10.5%), and lethargy (9.8%). The other symptoms observed in our study were arthralgia (9.5%), altered sensorium (7.8%), rash (7.2%), diarrhea (6.5%), oliguria (6.5%), cough/rhinitis (5.2%), anorexia (3.9%), and retro-orbital pain (1.3%). Important clinical signs were hepatomegaly and narrow pulse pressure. Details of clinical signs are shown in Fig. 2. Of 306 cases, 14% had complications, the most common complication being shock (9.9%), followed by severe gastrointestinal bleeding (4.4%), acute respiratory distress syndrome (4%), acute kidney injury (4%), acute hepatic failure (3%), and myocarditis (1.6%). There were 3 cases of intracranial bleed and 2 cases of dengue encephalitis in our study. Of the two cases of dengue encephalitis, we obtained IgG dengue positivity from CSF in one child whose CT brain showed hypodensities in bilateral thalami and cerebellar region (Fig. 3). The child presented with gaze palsy and extrapyramidal movements. MRI brain of the other child showed acute hemorrhagic leukoencephalitis. Both the children recovered completely.

Based on the clinical symptoms and signs, 131 (42.8%) were classified as dengue fever without warning signs, 119 (38.8%) as DWS, and 56 (18.4%) as SD, according to the WHO guidelines 2012. NS1 antigen was done in only 168 patients and was positive in 76% of cases. IgM dengue positivity was 90.8%. The investigation was not done in 9 cases as they got discharged before 5 days of onset of illness and was lost to follow-up. Even though 19 cases had negative IgM dengue, they fall into probable dengue according to the WHO criteria. Among 252 cases in which IgG was done, positivity was seen in 131 (42%) cases.

The liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated significantly in SD compared to non-SD (Table 1). 102 (33.3%) children had prolonged aPTT, while 64 (20.9%) had elevated prothrombin

time. The mean values of PT, INR, and aPTT in SD were 19±3.7 s, 1.5±0.3 s, and 46±7 s, respectively. These are well above the cutoff values and show statistically significant association with SD. Of the total cases, 14.1% had a platelet count <20,000 and low platelet count was significantly correlated with the severity of dengue (Table 2). The mean platelet recovery time was 2–5 days.

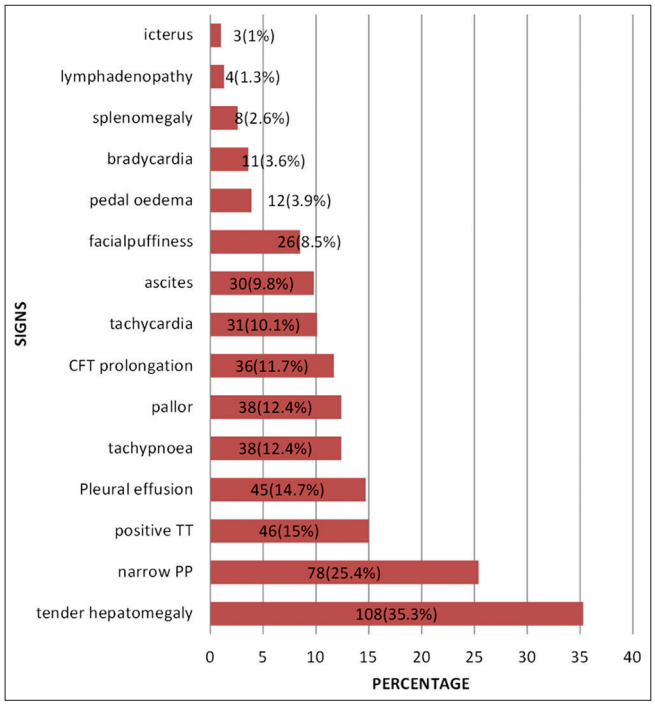

Figure 2: Bar chart demonstrating distribution of signs

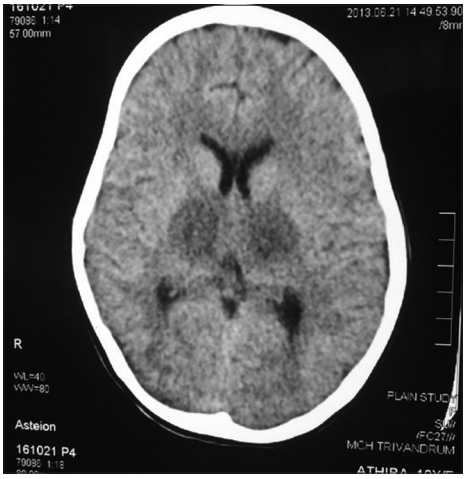

Figure 3: CT scan head showing bilateral thalamic hypodensity in a child with dengue encephalitis

The supportive measures used in the management of the study population included crystalloids (40.8%), colloids (11.4%), inotropes (8.8%), platelet transfusion (8.8%), packed red cells transfusion (8.8%), and fresh frozen plasma (7.5%). Mortality in the present study was 21 (7%). Among the cases who died of dengue fever, all had multi-organ dysfunction (100%) in the end. and the most common underlying predisposing conditions were acute respiratory distress syndrome (24%), refractory shock (24%), intracranial bleed (14%), massive gastrointestinal bleeding (14%), acute hepatic failure (14%), and myocarditis (10%). Of the total 306 cases, the subset in which IgG dengue was done (n=252) was classified as primary/secondary dengue based on IgM/IgG ratio. 193 cases (77%) were primary, and 59 (23%) were secondary. There was no statistically significant difference in clinical severity between primary and secondary dengue (p=0.15).

DISCUSSION

Of the 306 cases of children admitted with dengue fever, 131 (42.8%) were dengue fever without warning signs, 119 (38.8%) were DWS, and 56 (18.4%) were SD according to the WHO guidelines 2012. Majority of the studies on dengue fever are based on previous the WHO classification as dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Only a few studies are there in the literature based on latest WHO guidelines [5]. In the study conducted by Sahana and Sujatha, of the total 81 children, only 39 (48.1%) had dengue fever without warning signs, 22 (27.2 %) had DWS, and 20 (24.7 %) patients had SD [8]. We observed that majority of the cases in our study belonged to the age group of 6–12 years (57%) and the proportion of infants was 16%. This was in accordance with other studies [8,9]. In the study conducted by Mittal *et al*., 68% cases were in the age group of 6–12 years, only 2.9% were infants and the mean age group was 8.3±3.5 years [9]. There was a slight male preponderance (male:female ratio - 1.06:1). Batra *et al*. reported a close figure of male:female ratio as our study (1.08:1) [10]. The covered clothing in a female may offer some protection from mosquito bite. However, Ratageri *et al*. noticed a male:female ratio of 0.92:1 [11]. The assessment of nutritional status of children in our study revealed that 70.6% had normal weight for age. Dengue fever did not occur in children beyond Grade II underweight in our study. Most of the cases of SD (69.9%) had normal weight. The literature also showed that dengue virus

Table 1: Liver enzymes and coagulation profile in subtypes of dengue fever

Parameters	Reference value	DNW (%)	DWS (%)	SD (%)	p
PT	>16	3 (2.30)	14 (11.80)	47 (83.90)	
INR	>1.1	29 (22)	71 (59.7)	54 (96.40)	
aPTT	>38	10 (7.60)	41 (34.50)	51 (91.10)	
AST	>400	6 (4.6)	10 (8.4)	33 (58.9)	<0.001
ALT	>400	2 (1.5)	4 (3.4)	46.4 (32)	<0.001

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, DNW: Dengue without warning sign, DWS: Dengue with warning sign, SD: Severe dengue

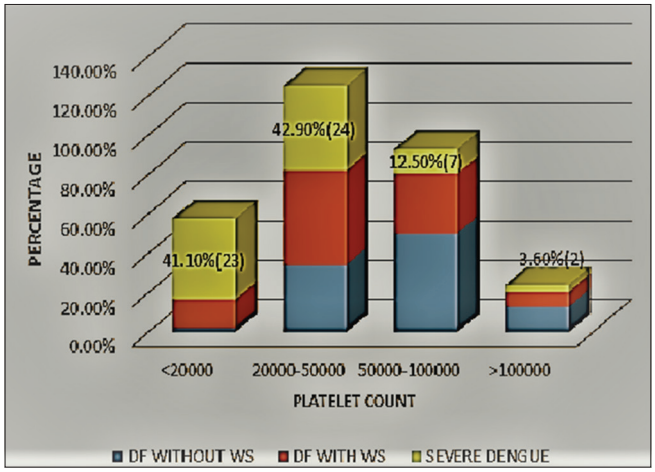

Figure 4: Compound bar diagram showing distribution of platelet count in the subgroups of dengue fever

Table 2: Summary of baseline characteristics of severe and non-SD

Characteristics	Severe (n=56)	Non-SD (n=250)	p**
Age (mean±SD) (years)	6.9±3.7	6.9±4.1	
Male sex (%)	48.2	52.4	
Vomiting (%)	68.9	52	
Abdominal pain (%)	62.5	30.4	
Bleeding manifestations (%)	53.6	6.8	
Tender hepatomegaly (%)	75	26.4	
Positive tourniquet test (%)	15	12.4	
Laboratory parameters (mean±SD)			
Hb	13±2.5	12±1.5	0.012
PCV	44±4	35±4	0.003
Platelet count	30980±2465	61820±7620	0.003
Bilirubin	0.7±0.3	0.5±0.2	<0.001
SGOT	1835±228	182±43	<0.001
SGPT	920±115	98±27	<0.001
Total protein	5±1.5	6.3±0.8	<0.001
Serum albumin	2.8±0.6	3.5±0.4	<0.001
Blood urea	35±2	19±0.7	<0.001
Serum creatinine	0.7±0.2	0.6±0.1	<0.001
Sodium	133±5	134±3	0.190
Potassium	4±0.6	4±0.5	0.019
Calcium	7.3±1.8	8.8±0.8	<0.001
Random blood sugar	65±6	85±4	<0.001

SGPT: Serum glutamic pyruvic transaminase, Hb: Hemoglobin, SGOT: Serum glutamate oxaloacetate transaminase, SD: Standard deviation, non-SD: Non-severe dengue, PCV: Packed cell volume, **: ???

infection is more severe among children with better nutritional status [12,13]. Children with good nutritional status can mount stronger immune response and have a higher risk of developing severe clinical manifestations.

The most common symptoms in dengue fever following fever were vomiting (54.9%) and abdominal pain (36.3%). The proportion of cases with vomiting and abdominal pain in the study conducted by Karoli *et al*. and Jhamb *et al*. were 63%, 58% and 61%, 51%, respectively [14,15]. The proportion of headache and bleeding manifestations was only 13.4% and 14.05%, respectively, while other studies showed higher incidence of the same. In the study by Mittal *et al*., the proportion of headache and bleeding manifestations was 63% and 48%, respectively [9]. Arti *et al*. reported 10% of altered sensorium almost similar to our study [16]. Ratageri *et al*. reported that 87% had hepatomegaly and 23% had signs of fluid retention [11]. Our study revealed icterus only in 1% of cases. Roy *et al*. reported an incidence of 60% of icterus in their study while other studies reported lower incidence of jaundice similar to our study [17]. Lymphadenopathy was observed in a minor proportion of cases (1.3%). It was only reported in some studies describing the rare manifestation of hypoplastic left heart syndrome in dengue [18]. In our study, one of the two cases of dengue encephalitis, we obtained IgG dengue positivity from CSF. The same was not reported in the literature, though similar clinical observations were found in many studies [17,18].

Mortality in the present study was 7% (21 cases). Of the 56 cases of SD, 37.5% succumbed. The case fatality rate of dengue among SD was 7.9% in the study conducted by Campos *et al*. Moraes *et al*. also reported a similar figure of 8.6% mortality in SD cases. Juneja *et al*. reported a mortality rate of 6.1% among SD cases [19-21]. Van Gorp *et al*. reported a mortality rate of 26% among SD in their study [7]. This was the only study with a comparable mortality rate as our study. The mortality rate among SD was higher in our study, probably because, our hospital being a tertiary care center received cases of refractory complications from all the hyperendemic dengue areas in the vicinity and late referral from the periphery also added on. All the deaths in our study were due to multiorgan dysfunction.

In the study by Kassim *et al*., 32.2% of the samples were found positive for dengue NS1 antigen, 40.9% were IgM positive, and 36.1% were IgG positive for dengue virus [22]. Similarly, Sahana *et al*. study showed less number of IgM, IgG antibody, and 66.7% NS1 antigen positive. Our study showed higher yield for the serological markers compared to the previous study. When more number of cases are clinically diagnosed and subjected for antibody test, the percentage of positivity increases. The 19 cases who were IgM negative had all the clinical criteria for dengue as per the WHO guidelines 2012 and hence were included as probable dengue (dengue fever without warning signs).

The detailed analysis of coagulation markers in our study is given in Table 1. This observation was important as impaired fibrinolysis and coagulation are considered to be a potential pathogenic mechanism of SD [23]. Khalil *et al*. showed coagulopathy as a significant risk factor for mortality as well [24]. The study conducted by Van Gorp *et al*. and Isangkura *et al*. also showed similar results [7,25]. We observed that 90.8% had platelet count <100,000 and 14.1% had platelet count <20,000. Of the 56 cases of SD, 41.1% had a platelet count <20000 (Fig. 4). In the study by Mittal *et al*., 82% had thrombocytopenia and is comparable to our study [9].

The hepatic involvement of dengue in our study is evidenced by the elevation of hepatic transaminases. Statistical analysis

showed a significant difference in AST and ALT elevation among dengue fever without warning signs, DWS and SD ($p<0.001$). This was in accordance with other studies [9,17]. Of 306 cases, platelet recovery time was analyzed in 268 cases after excluding those who had platelet count >100,000 and those who did not survive. 85.1% had platelet recovery time between 2 and 5 days. Mittal *et al*. observed that mean platelet recovery time to be 3.6±1.3 days and is comparable to our study. Among SD cases, also majority (64%) fell in between 2 and 5 days. In our study, 72% had a duration of hospitalization <5 days. This was in accordance with Mittal *et al.* in which mean duration of hospitalization was 4.2±2.3 days [9].

We further classified the study population into two groups: Severe and non-SD. The latter comprises cases of DWS and dengue fever without warning signs (n=250). The baseline characteristics - demographic, clinical, and laboratory findings - of the two groups were compared (Table 2). It was observed that the mean age and gender distribution in both groups were almost similar. The incidence of vomiting, abdominal pain, bleeding manifestations, tender hepatomegaly, and positive tourniquet test was more in SD cases. Hemoconcentration, thrombocytopenia, hypoproteinemia, hypoalbuminemia hypocalcemia, hypoglycemia, hypokalemia, hepatic derangement, elevated urea, and creatinine were significantly associated with SD. The markers of coagulation were significantly prolonged in SD group ($p<0.001$). These findings were consistent with similar comparative study between survivors and non-survivors in a study by Von Gorp *et al*. [7]. Thus, the role of coagulation profile as a marker of severity in dengue is reinforced in our study.

On comparing the clinical severity in primary and secondary dengue, there was no significant difference among the proportion of the WHO subgroups of dengue cases. This was in contrast to the immune pathogenesis of SD through antibody enhancement in secondary dengue. Our study supported the hypothesis of severity inflicted by virulent strains of dengue [26]. The study by Hati revealed that, in the age group of 1–10 years, more primary dengue cases are seen while secondary dengue cases are more in the elderly [27]. This observation also stands in support to our finding that there is no relation of primary/secondary cases with respect to severity in children.

The liver enzymes, coagulation parameters, and the platelet count in dengue fever change during the course of the disease. However, we have analyzed the value at admission which might have affected the value of the study. This we feel, is one important limitation of the study

CONCLUSION

Dengue fever occurs more in older children with better nutritional status and has a male predilection. Tender hepatomegaly, vomiting, and abdominal pain are the most common signs and symptoms, and they tend to occur in increased frequency in SD. There is a statistically significant association between prolongation of coagulation markers and hepatic transaminase levels with severity of dengue. Testing for liver enzymes and markers of coagulation can act as predictors of severity in dengue fever. There was no statistically significant difference in severity between children with primary and secondary dengue fever.

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